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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/065,311	10/02/2002	Svadovskiy Aleksandr Igorevich	1417.03	7689

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/065,311	IGOREVICH, SVADOVSKIY ALEKSANDR	
	Examiner	Art Unit	
	Christopher J Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☒ Claim(s) *5 and 6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the Russian Federation on 9 October 2001. It is noted, however, that applicant has not filed a certified copy of the RU 2001127259 application as required by 35 U.S.C. 119(b).

Claim Objections

2. Claims **1-6** are objected to because of the following informalities: claim numbering is not in a standard format. The claims must be numbered pursuant to MPEP §608.01(j)-(n) (i.e. "Claim 1 (Original)" not "[c1]"). Appropriate correction is required.

3. Claims **1-6** are objected to because of the following informalities: claims with multiple steps should follow the format pursuant to MPEP §608.01(n) (i.e. indenting after each step). Appropriate correction is required (see memo attached).

4. Claims **5** and **6** are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims **1, 2,** and **4** are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,690,915 (1 September 1987) Rosenberg and Silvani *et al.* (June 1994) "Successful Adoptive

Immunotherapy with Lymphokine-activated Killer Cells in the Treatment of Medulloblastoma Disseminated via Cerebrospinal Fluid: Case Report." Neurosurgery **34**(6): 1078-1081 in view of Svadovsky *et al.* (1995) "The properties and peculiarities of action of yeast recombinant IL-2 in combined treatment of brain gliomas." Journal of Neural Transmission: General Section **102**(3): XLVI.

6. US '915 teaches a therapeutic method for cancer including tumors comprising intravenous administration of lymphokine-activated killer (LAK) cells and 1,000 to 1,000,000 Units per Kg body weight of recombinant IL-2 to patients who had undergone surgical removal of their tumors as well as biopsies thus meeting the limitations of claims 1 and 4 (Col. 1 lines 1-15; Figure 2; Col. 3 lines 60-67; Col. 4 lines 1-55; Col. 5 lines 9-15). US '915 teaches administration of said therapy wherein the intravenous prolonged infusion was substantially between 1 to 3 days meeting the limitations of claim 2 (see Figure 3 and Col. 2 lines 25-45; Col. 11 line 6). This combination of LAK cells and IL-2 is generally referred to as "adoptive immunotherapy" in the art.

7. Silvani *et al.* teaches a method of treating medulloblastoma (a type of intracranial tumor) via adoptive immunotherapy: a combination of LAK cells and 10,000 to 300,000 IU of recombinant human IL-2 administration (Table 1). This treatment was after surgery to remove the medulloblastoma and biopsies to study them thus meeting the limitations of claims 1 and 4 (pp. 1078).

8. Svadovksy *et al.* teaches a method of treating brain gliomas (a type of intracranial tumor) via adoptive immunotherapy: a combination of LAK cells and recombinant yeast IL-2 administration. This treatment was after surgery to remove the gliomas and biopsies to study

them thus meeting the limitations of claims 1 and 4. The Examiner notes that "recombinant yeast interleukin-2" may be interpreted in one of two ways. The first interpretation is that the gene itself is yeast in origin and the second is that the gene is produced by a yeast host such as *Saccharomyces cerevisiae*. As IL-2 is a mammalian and not a yeast (or fungi) gene, the second interpretation has been adopted.

9. Applicant's inventive contribution in claims 1, 2, and 4 is two fold: first the use of "recombinant yeast interleukin-2" and second administration as "prolonged infusion". However, it would have been obvious for a person of ordinary skill in the art at the time of the invention to combine the teachings of US '915 with Silvani *et al.* and Svadovsky *et al.* because US '915 teaches that adoptive immunotherapy works where traditional treatments, including surgery (resection) and chemotherapy have failed (Col. 1 lines 1-63).

10. A person of ordinary skill in the art at the time of the invention would have been motivated to combine the teachings of US '915 with the therapy of Silvani *et al.* and Svadovsky *et al.* because Silvani *et al.* teaches that traditional treatment, including surgery and chemotherapy, of primary malignant intracranial tumors has been unsuccessful and the adoptive immunotherapy has been successful (pp. 1078). Secondly, Svadovsky *et al.* teaches that recombinant yeast IL-2 easily crosses the blood brain barrier, a significant advantage in brain treatment strategies. In fact, Silvani *et al.* notes the lack of considerable side effects and the persistence of clinical well being and negative CSF examinations 30 months after the therapy as additional motivation to use adoptive immunotherapy to treat intracranial tumors (pp. 1080).

11. A person of ordinary skill in the art at the time of the invention would have a reasonable expectation of success because Silvani *et al.* and Svadovsky *et al.* both teach that adoptive

immunotherapy was successful for medulloblastomas and brain gliomas. In addition, Silvani *et al.* teaches that adoptive immunotherapy was successful in treating medulloblastomas where other therapies failed.

12. Claims **1, 2,** and **4** are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,690,915 (1 September 1987) Rosenberg and Silvani *et al.* (June 1994) "Successful Adoptive Immunotherapy with Lymphokine-activated Killer Cells in the Treatment of Medulloblastoma Disseminated via Cerebrospinal Fluid: Case Report." Neurosurgery **34**(6): 1078-1081 in view of Miyajima & Arai (1989) "Use of a cDNA Expression-Cloning Vector and a Secretion Vector for Mammalian Gene Expression in *Saccharomyces cerevisiae.*" Biotechnology **13**(Chapter 15): 281-304.

13. US '915 teaches a therapeutic method for cancer including tumors comprising intravenous administration of lymphokine-activated killer (LAK) cells and 1,000 to 1,000,000 Units per Kg body weight of recombinant IL-2 to patients who had undergone surgical removal of their tumors as well as biopsies thus meeting the limitations of claims 1 and 4 (Col. 1 lines 1-15; Figure 2; Col. 3 lines 60-67; Col. 4 lines 1-55; Col. 5 lines 9-15). US '915 teaches administration of said therapy wherein the intravenous prolonged infusion was substantially between 1 to 3 days meeting the limitations of claim 2 (see Figure 3 and Col. 2 lines 25-45; Col. 11 line 6). This combination of LAK cells and IL-2 is generally referred to as "adoptive immunotherapy" in the art.

14. Silvani *et al.* teaches a method of treating medulloblastoma (a type of intracranial tumor) via adoptive immunotherapy: a combination of LAK cells and 10,000 to 300,000 IU of

recombinant human IL-2 administration (Table 1). This treatment was after surgery to remove the medulloblastoma and biopsies to study them thus meeting the limitations of claims 1 and 4 (pp. 1078).

15. Miyajima & Arai teaches a method of expressing and purifying human IL-2 in yeast cells (pp. 294 and 301). The Examiner notes that "recombinant yeast interleukin-2" may be interpreted in one of two ways. The first interpretation is that the gene itself is yeast in origin and the second is that the gene is produced by a yeast host such as *Saccharomyces cerevisiae*. As IL-2 is a mammalian and not a yeast (or fungi) gene, the second interpretation has been adopted.

16. Applicant's inventive contribution in claims 1, 2, and 4 is two fold: first the use of "recombinant yeast interleukin-2" and second administration as "prolonged infusion". However, it would have been obvious for a person of ordinary skill in the art at the time of the invention to combine the teachings of US '915 with Silvani *et al.* and Miyajima & Arai because US '915 teaches that adoptive immunotherapy works where traditional treatments, including surgery (resection) and chemotherapy have failed.

17. A person of ordinary skill in the art at the time of the invention would have been motivated to combine the teachings of US '915 with the therapy of Silvani *et al.* because Silvani *et al.* teaches that traditional treatment, including surgery and chemotherapy, of primary malignant intracranial tumors has been unsuccessful and the adoptive immunotherapy has been successful. Miyajima & Arai teaches that human IL-2 expressed in yeast cells are glycosylated which is required for full biological activity of IL-2, a significant advantage in brain treatment strategies (see below). Also Silvani *et al.* teaches that adoptive immunotherapy was successful in treating medulloblastomas where other therapies failed. In fact, Silvani *et al.* notes the lack of

considerable side-effects and the persistence of clinical well-being and negative CSF examinations 30 months after the therapy as additional motivation to use adoptive immunotherapy to treat intracranial tumors (pp. 1080).

18. A person of ordinary skill in the art at the time of the invention would have a reasonable expectation of success because Silvani *et al.* teaches that adoptive immunotherapy was successful in treating medulloblastomas where other therapies failed.

19. Claims **1, 2, 3,** and **4** are rejected under 35 U.S.C. 103(a) as being unpatentable over Silvani *et al.* (June 1994) "Successful Adoptive Immunotherapy with Lymphokine-activated Killer Cells in the Treatment of Medulloblastoma Disseminated via Cerebrospinal Fluid: Case Report." Neurosurgery **34**(6): 1078-1081 and US 5,002,879 (26 March 1991) Bowlin *et al.* in view of Miyajima & Arai (1989) "Use of a cDNA Expression-Cloning Vector and a Secretion Vector for Mammalian Gene Expression in *Saccharomyces cerevisiae*." Biotechnology **13**(Chapter 15): 281-304.

20. Silvani *et al.* teaches a method of treating medulloblastoma (a type of intracranial tumor) via adoptive immunotherapy: a combination of LAK cells and 10,000 to 300,000 IU of recombinant human IL-2 administration (Table 1). This treatment was after surgery to remove the medulloblastoma and biopsies to study them thus meeting the limitations of claims 1 and 4 (pp. 1078).

21. US '879 teaches that administration of IL-2 intravenously is preferable once every day or for from 1 to 5 daily doses, slowly infusing the IL-2 over the period of 60 minutes, for 2 to 5 days thus meeting the limitations of claims 2 and 3 (Col. 3 lines 55-67; Col. 4 lines 1-30).

22. Miyajima & Arai teaches a method of expressing and purifying human IL-2 in yeast cells (pp. 294 and 301). The Examiner notes that "recombinant yeast interleukin-2" may be interpreted in one of two ways. The first interpretation is that the gene itself is yeast in origin and the second is that the gene is produced by a yeast host such as *Saccharomyces cerevisiae*. As IL-2 is a mammalian and not a yeast (or fungi) gene, the second interpretation has been adopted.

23. Applicant's inventive contribution in claims 1, 2, 3, and 4 is two fold: first the use of "recombinant yeast interleukin-2" and second administration as "prolonged infusion". However, it would have been obvious for a person of ordinary skill in the art at the time of the invention to combine the teachings of Silvani *et al.* with US '879 and Miyajima & Arai because Silvani *et al.* teaches that adoptive immunotherapy works where traditional treatments, including surgery (resection) and chemotherapy have failed.

24. A person of ordinary skill in the art at the time of the invention would have been motivated to combine the teachings of Silvani *et al.* with US '879 and Miyajima & Arai because Silvani *et al.* teaches that traditional treatment, including surgery and chemotherapy, of primary malignant intracranial tumors has been unsuccessful and the adoptive immunotherapy has been successful. In addition, US '879 teaches that slow (prolonged) infusion (via intravenous administration) of IL-2 is preferable to avoid the considerable side-effects usually associated with IL-2. Miyajima & Arai teaches that human IL-2 expressed in yeast cells are glycosylated which is required for full biological activity of IL-2, a significant advantage in brain treatment strategies (see below).

25. A person of ordinary skill in the art at the time of the invention would have a reasonable expectation of success because Silvani *et al.* teaches that adoptive immunotherapy was successful in treating medulloblastomas where other therapies failed.

Summary

26. No claims are allowed.

27. Examiner notes that Surgeon's goal is total removal of tumor. As such, unless otherwise stated all "resections" are taken to be "total" in that the surgeon removes the entire tumor to the best of their ability. The American Heritage Dictionary of the English Language (2002) defines "resection" as "Surgical removal of all or part of an organ, tissue, or structure." (Internet 3.3.05)

28. The Examiner notes that lymphokine-activated killer cells (LAK) are defined in the art by US 5,108,760 (28 April 1992) Irr & Leung: "Incubation of Interleukin-2 (IL-2) with human peripheral blood mononuclear cells (PBMC) or mouse splenocytes induces a population of highly tumoricidal cells. This phenomenon has been referred to as lymphokine activated killer (LAK) cell activity." (Col. 1 lines 12-18)

29. The Examiner notes that 18 million international units (MU) is equivalent to about 1 mg of IL-2 protein [see US 6,190,656 B1 (20 February 2001) Lane *et al.*(Col. 1 lines 62-67, Col. 2 lines 1-4)].

30. As discussed above by the Examiner, recombinant proteins produced in prokaryotic cell lines such as *E. coli* are not glycosylated while those produced by eukaryotic cell lines such as yeast are glycosylated [see Oosterhout and Nijkamp (1990) "Effect of Human Interleukin-2 from

Different Sources on Lymphoctye and Airway β-Adrenoceptor Function." Int. J. Immunopharmc. **12**(4): 409-412 teaches that (Tables 1 & 2; pp. 412).]

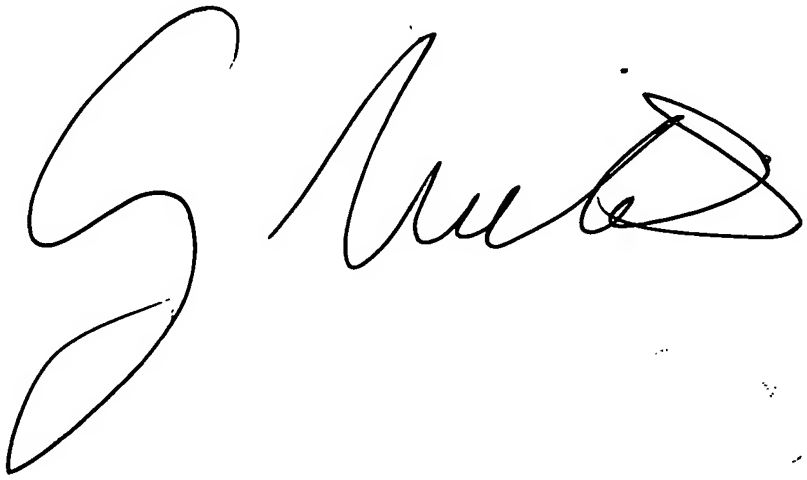
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback** can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

CJN
March 3, 2005



Revised Notice*
AMENDMENTS MAY NOW BE SUBMITTED IN REVISED FORMAT

The United States Patent and Trademark Office (USPTO) is permitting applicants to submit amendments in a revised format as set forth below. Further details of this practice are described in *AMENDMENTS IN A REVISED FORMAT NOW PERMITTED*, signed January 31, 2003, expected to be published in *Official Gazette* on February 25, 2003 (Notice posted on the Office's web site at http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). The revised amendment format is essentially the same as the amendment format that the Office is considering adopting via a revision to 37 CFR 1.121 (Manner of Making Amendments). The revision to 37 CFR 1.121 (if adopted) will simplify amendment submission and improve file management. The Office plans to adopt such a revision to 37 CFR 1.121 by July of 2003, at which point compliance with revised 37 CFR 1.121 will be mandatory.

Effective immediately, **all** applicants may submit amendments in reply to Office actions using the following format. Participants in the Office's electronic file wrapper prototype[1] receiving earlier notices of the revised practice may also employ the procedures set out below.

REVISED FORMAT OF AMENDMENTS

Begin on separate sheets:
Each section of an Amendment (e.g., Claim Amendments, Specification Amendments, Drawing Amendments, and Remarks) should begin on a separate sheet. *For example*, in an amendment containing a.) introductory comments, b.) amendments to the claims, c.) amendments to the specification, and d.) remarks, each of these sections must begin on a separate sheet. This will facilitate the process of separately indexing and scanning of each part of an amendment document for placement in an electronic file wrapper.

Two versions of amended part(s) no longer required:
The current requirement in 37 CFR 1.121(b) and (c) to provide two versions (a clean version and a marked up version) of each replacement paragraph, section or claim will be waived where an amendment is submitted in revised format below. The requirements for substitute specifications under 37 CFR 1.125 will be retained.

A) Amendments to the claims:
Each amendment document that includes a change to an existing claim, or submission of a new claim, **must include a complete listing** of all claims in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.

(1) The current status of all of the claims in the application, including any previously canceled or withdrawn claims, must be given. Status is indicated in a parenthetical expression following the claim number by one of the following: (original), (currently amended), (previously amended), (canceled), (withdrawn), (new), (previously added), (reinstated – formerly claim #_), (previously reinstated), (re-presented – formerly dependent claim #_), or (previously re-presented). The text of all pending claims under examination must be submitted each time any claim is amended. Canceled and withdrawn claims should be indicated by only the claim number and status.

(2) All claims being currently amended must be presented with markings to indicate the changes that have been made relative to the immediate prior version. The changes in any amended claim should be shown by strikethrough (for deleted matter) or underlining (for added matter). An accompanying clean version is not required and should not be presented. Only claims of the status "currently amended" will include markings.

(3) The text of pending claims not being amended must be presented in clean version, i.e., without any markings. Any claim text presented in clean version will constitute an assertion that it has not been changed relative to the immediate prior version.

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[1] The Office's Electronic File Wrapper prototype program is described in *USPTO ANNOUNCES PROTOTYPE OF IMAGE PROCESSING*, 1265 *Off. Gaz. Pat. Office* 87 (Dec. 17, 2002) ("Prototype Announcement"), and applies only to Art Units 1634, 2827 and 2834.

(4) A claim may be canceled by merely providing an instruction to cancel. Listing a claim as canceled will constitute an instruction to cancel. Any claims added by amendment must be indicated as (new) and shall not be underlined.
(5) All of the claims in each amendment paper must be presented in ascending numerical order. Consecutive canceled or withdrawn claims may be aggregated into one statement (e.g., Claims 1 – 5 (canceled)).

Example of listing of claims (use of the word "claim" before the claim number is optional):

Claims 1-5 (canceled)

Claim 6 (withdrawn)

Claim 7 (previously amended): A bucket with a handle.

Claim 8 (currently amended): A bucket with a ~~green~~ blue handle.

Claim 9 (withdrawn)

Claim 10 (original): The bucket of claim 8 with a wooden handle.

Claim 11 (canceled)

Claim 12 (re-presented – formerly dependent claim 11) A black bucket with a wooden handle.

Claim 13 (previously added): A bucket having a circumferential upper lip.

Claim 14 (new): A bucket with plastic sides and bottom.

B) Amendments to the specification:
Amendments to the specification must be made by presenting a replacement paragraph or section marked up to show changes made relative to the immediate prior version. An accompanying clean version is not required and should not be presented. If a substitute specification is being submitted to incorporate extensive amendments, both a clean version (which will be entered) and a marked up version must be submitted as per current 37 CFR 1.125.

C) Amendments to drawing figures:
Drawing changes must be made by presenting replacement figures which incorporate the desired changes and which comply with § 1.84. An explanation of the changes made must be presented in the remarks section of the amendment. Any replacement drawing sheet must include all of the figures appearing on the immediate prior version of the sheet, even though only one figure may be amended. The figure or figure number of the amended drawing should **not** be labeled as "amended." If the changes to the drawing figure(s) are not accepted by the examiner, applicant will be notified of any required corrective action in the next Office action. No further drawing submission will be required, unless applicant is notified.

Any questions regarding the submission of amendments pursuant to the revised practice set forth in this flyer should be directed to the following legal advisors in the Office of Patent Legal Administration (OPLA): Elizabeth Dougherty (Elizabeth.Dougherty@uspto.gov), Gena Jones (Eugenia.Jones@uspto.gov) or Joe Narcavage (Joseph.Narcavage@uspto.gov). For information on the waiver or legal aspects of the prototype, please contact Jay Lucas (Jay.Lucas@uspto.gov), Senior Legal Advisor (PCTLA) or Rob Clarke (Robert.Clarke@uspto.gov), Senior Legal Advisor (OPLA). Alternatively, further information may be obtained by calling OPLA at (703) 305-1616.

* Revised Notice: See Sec. B) for changes relating to substitute specifications, and Sec. C) for changes on replacement drawing practice.